E PPAR GAMMA LIGAND ELUTING STENT

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INVENTION: I DISCLOSE A MODIFICATION TO A STENT DESIGNED TO IMPROVE THE TREATMENT OF RESTENOSIS BY ELUTING LIGANDS OF PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR GAMMA (PPARγ) FROM THE STENT. IN ITS SIMPLEST EMBODIMENT, A SINGLE PPARγ LIGAND IS ADDED TO A STENT BEFORE IMPLANTATION IN A PHARMACEUTICALLY SUFFICIENT DOSE & WITH SUFFICIENT DURATION OF ELUTION TO BLOCK THE LOCAL INCIDENCE OF RESTENOSIS AFTER STENT DEPLOYMENT IN THE BODY.

RATIONALE FOR CHOOSING PPARγ LIGANDS: PPARγ IS A MEMBER OF A NUCLEAR RECEPTOR SUPERFAMILY THAT IS ACTIVATED BY BINDING CERTAIN LIGANDS. THESE LIGANDS CAN BE CHOSEN FROM CERTAIN FATTY ACIDS, EICOSANOIDS AND INSULIN-SENSITIZING THIAZOLIDINEDIONES. SEVERAL PHARMACEUTICAL DRUGS ARE PART OF THIS LATTER CLASS: ROSIGLITAZONE, PIOGLITAZONE & TROGLITAZONE.

AN IMPORTANT CHARACTERISTIC OF ANTI-RESTENOTIC ~~DRUGS~~ AGENTS IS THEIR ABILITY TO INHIBIT SMOOTH MUSCLE CELL (SMC) PROLIFERATION. PPARγ LIGANDS ARE KNOWN TO INHIBIT VASCULAR SMC PROLIFERATION PROBABLY BY DIRECT INHIBITION OF CYCLIN-DEPENDENT KINASES (1, 2).

A SECOND PROPERTY KEY IN AN ANTI-RESTENOTIC AGENT IS INHIBITION OF SMC MIGRATION (eg FROM THE MEDIA TO THE NEOINTIMA OF AN ARTERY). PPARγ LIGANDS BLOCK MIGRATION OF VASCULAR SMCs (1).

A THIRD PROPERTY FOR AN ANTI-RESTENOTIC AGENT IS ITS ABILITY TO BLOCK LOCAL INVASION/ACTIVATION OF MONOCYTES &/OR THEIR ENSUING SECRETION OF GROWTH FACTORS/CYTOKINES WHICH PRESUMABLY TRIGGER SMC ENTRY INTO THE CELL CYCLE. PPARγ AGONISTS INHIBIT MIGRATION OF MONOCYTES (33) & CYTOKINE PRODUCTION BY MONOCYTES (34). INTERESTINGLY, IT IS KNOWN THAT CERTAIN NON-STEROIDAL ANTI-INFLAMMANT DRUGS (NSAIDs) LIKE SULINDAC ARE ANTI-RESTENOTIC IN PIGS WITH PLAQUE-LIKE LESIONS (4). THIS COULD BE RELATED TO THE FACT THAT NSAIDs HAVE PPARγ AGONIST ACTIVITY AT HIGH CONCENTRATIONS (5).

RECENT CLINICAL FINDINGS DEMONSTRATE THAT PATIENTS DOSED SYSTEMICALLY WITH TROGLITAZONE HAVE REDUCED NEOINTIMAL PROLIFERATION AT SIX-MONTHS AFTER CORONARY STENT IMPLANTATION (6). UNFORTUNATELY THIS DRUG, UNDER THE TRADE NAME REZULIN WAS RECENTLY WITHDRAWN FROM USE IN TREATING TYPE II DIABETICS BECAUSE OF EXCESSIVE LIVER TOXICITY. SINCE PLASMA DRUG LEVELS WERE SIMILAR IN BOTH CASES, IT IS LIKELY THAT THE ANTI-RESTENOTIC EFFECTS OF SYSTEMIC TROGLITAZONE COULD ALSO LEAD TO

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Witnessed & Understood by me,

Invented by ROBERT L. CAPPELLETTA

Recorded by

DEATHS FROM LIVER TOXICITY. ONE OF THE PURPOSES OF THE PRESENT INVENTION IS REDUCE THE DOSE & BIODISTRIBUTION OF THIS DRUG BY ELUTING IT LOCALLY FROM A STENT WITHIN THE BODY LUMEN BEING TREATED FOR RESTENOSIS.

METHODS FOR COMBINING PHARMACEUTICAL DOSAGE FORMS ONTO IMPLANTABLE DEVICES STENTS:

- PRECIPITATION, COACERVATION, CRYSTALLIZATION OF DRUG ONTO THE SURFACE OF STENT (OR WELLS/CHANNELS PLACED IN THE BODY OF THE STENT AS DRUG RESERVOIR CHANNELS) & ACT AS A DIFFUSION-BARRIER TO CONTROL RELEASE OF DRUG
- ADDITION TO THE MATERIAL USED TO COMPOUND ERODIBLE POLYMERIC STENTS.
- CONTACT WITH CHEMICALLY REACTIVE SURFACES (FILMS) BONDED TO THE SURFACE THE STENT. ONE SUCH EXAMPLE WAS ANTICIPATED IN RAPID IN-SITU RELEASING "DRUG" IMPLANT (pp 7-11).

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